UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,038	07/10/2000	Antonio J. Grillo-Lopez	P1752R1	9334

7590 02/14/2002

Attn Wendy Lee
1 DNA Way
South San Francisco, CA 94080-4990

EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,038	GRILLO-LOPEZ ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *3,17-19,21,24-27 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-16,20,22,23,28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5-8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' election of species (d) where the foreign antigen is a graft without traverse in Paper No. 10 is acknowledged.

Claims 1-28 and 30-31 are pending in the present application. Claims 3, 17-19, 21, 24-27 and 31 are withdrawn from further consideration because they are not drawn to the elected species. It is noted that as defined by the present application, a "therapeutic agent" refers to a compound or a composition which is used to treat a disease or disorder in a patient; and a therapeutic agent may comprise a polypeptide such as an antibody, a toxin, a gene therapy viral vector and/or a hemophilic factor (page 5, lines 9-13). Meanwhile, "a graft" refers to biological material derived from a donor for transplantation into a recipient, and it includes isolated cells such as islet cells; tissue such as amniotic membrane of a newborn, bone marrow, hematopoietic precursor cells; organs such as skin, heart, liver, spleen and others (page 6, lines 15-25).

Accordingly, claims 1-2, 4-16, 20, 22-23, 28 and 30 are examined on the merits herein.

Information Disclosure Statement

Most of the references cited in the IDS filed Nov 20, 2000 in Paper No. 5 have not been considered because they are not present in the application. Applicant is requested to provide the missing references.

Claim Objections

Claims 13-15 are objected to because of the following informalities: There should be a space between 375 or 250 or 200 and the term "mg/m^{2}". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-16, 20, 22-23, 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of blocking an immune response to a foreign antigen in a mammal wherein the mammal is not suffering from a malignancy, comprising administering to the mammal a therapeutically effective amount of an antagonist which binds to CD20. The instant claimed invention is also drawn to a method of treating graft-versus-host or host-versus-graft disease in a mammal utilizing a therapeutically effective amount of an antagonist which binds to CD20; and an article comprising composition containing an antagonist which binds to CD20. The claims encompass the utilization of any antagonist molecule (an antibody or a synthetic or native sequence peptide or small molecule antagonist) which upon binding to CD20 destroys or depletes B cells in a mammal to reduce or prevent a humoral response elicited by the B cells. However, apart from the disclosure of rituximab (RITUXAN) the instant disclosure fails to provide a representative number of species of antagonist that is capable of binding to CD20 to destroy and/or deplete B cells in a mammal to reduce effectively a humoral response against any foreign antigen or for treating any graft-versus-host or host-versus-graft disease. It is also unclear which essential core structural elements that are shared among the CD20 antagonists encompassed by the broad scope of the instant claimed invention to yield the desired therapeutic results contemplated by Applicants (e.g., blocking an immune response to a foreign antigen, treating graft-versus-host or host-versus-graft disease) other than the common functional limitation of binding to CD20. The prior art at about the effective filing date of the present application does not provide such guidance. The claimed invention as a whole is not adequately described if the claims require essential or critical elements

which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of any antagonist which binds to CD20 to yield therapeutic results contemplated by Applicants apart from the antibody rituximab or RITUXAN, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-2, 4-16, 20, 22-23, 28 and 30 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1-2, 4-16, 20 and 22-23 are drawn to a method of blocking an immune response to a foreign antigen in a mammal, wherein the mammal is not suffering from a malignancy, comprising administering to the mammal a therapeutically effective amount of an antagonist which binds to CD20.

Claim 28 is directed to a method of treating graft-versus-host or host-versus-graft disease in a mammal comprising administering to the mammal a therapeutically effective amount of an antagonist which binds to CD20.

Claim 30 is drawn to an article of manufacture comprising a container and a composition contained therein, wherein the composition comprises an antagonist which binds to CD20, and further comprising a package insert instructing the user of the composition to treat a patient who has been or will be exposed to a foreign antigen.

With respect to the elected species, the specification teaches a prophetic example in which an anti-CD20 antibody such as RITUXAN may contribute to the prevention of an allorejection response by inhibiting alloantibody production and/or

affecting alloantigen presentation through depletion of antigen-presenting cells. Applicants further teach that the anti-CD20 antibody may also be combined with other induction immunosuppressive drugs such as polyclonal anti-lymphocyte antibodies or monoclonal anti-CD3 antibodies; maintenance of immunosuppressive drugs, such as calcinuerin inhibitors, anti-proliferative agents or combination regimens that include blockade of T cell co-stimulation, blockade of T cell adhesion molecules and blockade of T cell accessory molecules.

The above evidence has been noted and considered. However, the instant specification is not enabled for the presently claimed invention for the reasons discussed below.

With respect to the breadth of the claims encompassing any antagonist that binds to CD20 to block an immune response to a foreign antigen or a graft as a selected species in a mammal to obtain the desired therapeutic effects, the instant specification is not enabled for such a broadly claimed invention for the reasons already stated in the Written Description above. Given the lack of sufficient guidance provided by the present disclosure, it would require undue experimentation for a skilled artisan to make and use the instant claimed invention.

When read in light of the specification, the instant claims encompass the reduction or prevention of at least one immune-mediated response resulting from the exposure of a mammal to a graft utilizing an effective amount of an antagonist which binds to CD20 (page 4, 27-28). At the effective filing date of the present application, apart from the utilization of rituximab, a chimeric murine-human monoclonal antibody

directed against CD20, for the treatment of B-cell lymphoma, the use of rituximab or any CD20 antagonist in other *in vivo* applications (e.g., graft transplantation) is still very limited and further investigation is required (Leget et al., Curr. Opin. Oncol. 10:548-551, 1998; IDS; Friend et al., Transplantation 68:1625-1631, 1999). With respect to the use of bio-engineered monoclonals in transplantations, Friend et al. stated "Monoclonal antibodies have proved to be of immense importance from a diagnostic and investigative standpoint. However in clinical transplantation their impact on therapeutic regimens have been rather disappointing" (page 1625, col.1, first paragraph). In light of the state of the art at the effective filing date of the present application, there is no evidence of record indicating or suggesting that the use of rituximab or any CD20 antagonist would be effective in reducing or preventing the host humoral and/or T cell-mediated immune responses against a graft (both allogeneic and xenogenic) to an extent that a graft would be survived and maintained for a sufficient period of time to yield any beneficial use or any graft versus host reactions. The instant specification offers no guidance regarding how to target rituximab specifically to a B cell population that produces alloantigen or xenoantigen antibodies against a graft or to a graft antigen presenting cell population or a donor T cell population in a graft such that these cell populations would be depleted or eliminated so that the desired therapeutic effects contemplated by Applicants could be achieved. Even in the B-cell lymphoma treatment studies with rituximab, despite the depletion of normal B cells, treated patients are still capable of eliciting an immune response against the humanized rituximab, even though it is at a low level (Leget et al., see abstract). Moreover, it is noted that rituximab has no

effect on the total mean serum IgG and IgA levels of patients treated with the humanized monoclonal antibody (Leget et al., page 550, col. 1, first paragraph; Levine et al., Neurology 52:1701-1704, 1999; IDS, see page 1704). Furthermore, Wilkes et al. (Transplantation Proceedings 29:1891-1895, 1997) disclose that the production of IgG2 antibodies plays an important role in human lung allograft rejection. As such, with the lack of any *in vivo* example (please note that it is part of a guidance), it is unclear whether the prevention or alleviation of any graft rejection to an extent to yield beneficial uses contemplated by Applicants could be attained. Therefore, it would require undue experimentation for a skilled artisan to make and use the instantly claimed invention.

The instant claims also encompass any route of administering an antagonist that binds to CD20 into a mammal not suffering from a malignancy to obtain the desired therapeutic effects. The instant specification is not enabled for such a broadly claimed invention because it offers no guidance on how to achieve the desired results via intravenous delivery of rituximab, let alone any route of delivery for any antagonist that binds to CD20 (e.g., oral, subcutaneous or mucosal deliveries). The prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so. With the lack of guidance provided by the present disclosure, it would require undue experimentation for one skilled in the art to make and use the claimed invention.

It should be further noted that physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 10, 13 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In both claims 7 and 10, it is unclear what is encompassed in the antibody with the trademark phrases "RITUXAN^{R}" and "BEXXAR^{TM}", respectively. The metes and bounds of the claims can not be clearly determined. To alleviate this rejection, the aforementioned trademark names should be deleted.

The term "a dose substantially less than 375mg/m^{2}" in claim 13 is a relative term which renders the claim indefinite. The term "a dose substantially less than 375mg/m^{2}" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Would a dose of 275 mg/m^{2}, 300

mg/m^2 or 325 mg/m^2 be considered to be substantially less than 375mg/m^2? The metes and bounds of the claim can not be clearly determined.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: the transplantation of a graft from a donor into a mammalian recipient either prior or after the administration of a therapeutically effective amount of an antagonist which binds to CD20. Otherwise, without a graft transplantation then how could there be any graft-versus-host or host-versus graft disease in a mammal, and there is a need for treatment? Clarification is requested.

In claim 30, it is unclear what is encompassed by the phrase "a package insert instructing the user of the composition to treat a patient who has been or will be exposed to a foreign antigen". What is included or not included in the instructing informations? The metes and bounds of the claim can not be clearly determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (U.S. Patent No. 5,736,137).

The claim is drawn to an article of manufacture comprising a container and a composition contained therein, wherein the composition comprises an antagonist which binds to CD20, and further comprising a packaging insert instructing the user of the composition to treat a patient who has been or will be exposed to a foreign antigen. It is noted that for a composition claim, its intended use is not given any patentable weight in light of the prior art.

Anderson et al. disclose a pharmaceutical composition comprising an immunologically active, chimeric mouse/human anti-CD20 antibody or the radiolabeled anti-CD20 antibody (an antagonist which binds to CD20) in a pharmaceutically acceptable carrier for the treatment of B cell lymphoma in a patient (see abstract and col. 8). Anderson et al. do not specifically teach that a pharmaceutical composition is contained within a container and that a package insert instructing the user of the composition is included along with the aforementioned container. However, it would have been obvious for an ordinary skilled artisan to provide the disclosed

pharmaceutical composition of Anderson et al. in a container (otherwise how would such a pharmaceutical composition be stored?) along with a set of instructions for the use of said pharmaceutical composition in the treatment of B cell lymphoma in a patient as intended by Anderson et al. One of ordinary skilled artisan would have been motivated to do so simply as a matter of a designer's choice to clearly instructing the proper use (e.g., dosages, frequency or route of administration) of the pharmaceutical composition for its intended application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

DAVE T. NGUYEN
PRIMARY EXAMINER